18/declaration 1.132

Application Serial No. 09/560,475 Atty. Docket No. 028870-178

Patent
Attorney's Docket No. 028870-178

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	
David C. Greenspan	Group Art Unit: 1615
Application No.: 09/560,475	Examiner: Amy E. Pulliam
Filed: April 28, 2000	Confirmation No.: 3797
For: Anti-Inflammatory Bioactive Glass Particulates	

DECLARATION UNDER 37 C.F.R. §.1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, David C. Greenspan, hereby state as follows:

EDUCATION AND BACKGROUND

1. I am an inventor in the above-identified application. I hold a B.S. in Glass Science from Alfred University (1972) and a Ph.D. in Materials Science from the University of Florida (1977). My Ph.D. thesis involved the development of bioactive glasses as coatings for orthopedic devices. I have over 35 publications in the area of bioactive glass research, and I hold 19 patents involving the use of bioactive glasses in the area of medical devices, including the areas of wound healing, bone regeneration and treatment of various oral health issues. I have worked in the field of biomaterials for most of the past 25 years.

PRODUCTION OF TNF-α

2. The attached exhibit A lists TNF-α proteins in the Entrez search and retrieval system of the National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health database of protein sequences.[1] In a search of this database for "tnf alpha" in the protein name, one *homo sapiens* TNF-α protein was identified, indicating that there is only one *homo sapiens* TNF-α protein in this exhaustive collection of databases.

3. The attached exhibit B, pages 677-679 from "Immunobiology" by Janeway *et al.*, is an appendix listing cytokines, cells which produce these cytokines, and their actions. On page 678, in the TNF family, the chart states that TNF-α is produced by macrophages, NK cells, and T cells in local inflammation and endothelial activation. At sites of inflammation throughout the body, TNF-α is produced by macrophages, NK cells, and T cells.

4. The claims define a method for minimizing the production of TNF-α caused by an inflammatory response in a patient comprising administering locally a locally effective TNF-α lowering amount of bioactive glass particles with a size less than about 20 μm to the patient. Example 2 describes that, upon intraperitoneal administration of bioactive glass to mice, IL-6 concentrations were increased, whereas the bioactive glass did not induce TNF-α. Example 2 further shows that peritoneal TNF-α was reduced in response to LPS by pretreatment with bioactive glass as claimed.

5. There is only one *homo sapiens* TNF-α protein, according to the Entrez search and retrieval system of the National Center for Biotechnology Information,

[1] The protein entries in the Entrez search and retrieval system have been compiled from a variety of sources, including SwissProt, PIR, PRF, PDB, and translations from annotated coding regions

National Library of Medicine, National Institutes of Health database of protein sequences. At sites of inflammation throughout the body, TNF-α is produced by macrophages, NK cells, and T cells. These cells which produce the TNF-α at one site of inflammation are the same cells which produce the TNF-α at another site of inflammation. In view thereof, the reduction of TNF-α upon administration of bioactive glass particles as shown in Example 2 in the peritoneal cavity will take place at any site in the patient.

THE BOSETTI ET AL. ARTICLE

6. I have read and understood the article entitled "Interaction of Bioactive Glasses with Peritoneal Macrophages and Monocytes *in vitro*", Bosetti et al., *Journal of Biomedical Materials Research*, 60(1): 79-85 (2002). Moreover, I am familiar with the bioactive glass material described in the Bosetti et al. article. Additionally, I have experience with a wide variety of sizes of particles of bioactive glass material. Upon information and belief, particles of the size claimed in present application, less than about 20 microns, will remain in the body at the site of administration less than three days, being resorbed into the body prior to that time. This is supported by the article in *Shock*, 17(2):135-138 (2002) submitted with Applicants' Amendment dated October 24, 2002.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under

in GenBank and RefSeq. The Entrez search and retrieval system is considered an authoritative resource by those of skill in the art.

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Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name: David C. Greenspan Date: June 10, 2003

Exhibit A

NCBI Entrez Protein

PubMed Nucleotide Protein Genome Structure PMC Taxonomy OMIM &c

Search Protein for tnf alpha Go Clear

Limits Preview/Index History Clipboard Details

About Entrez

Entrez Protein
Help | FAQ

Batch Entrez: Upload a file of GI or accession numbers to retrieve sequences

Check sequence revision history

How to create WWW links to Entrez

LinkOut

Cubby

Related resources
BLAST

Reference sequence project

LocusLink

Clusters of orthologous groups

Protein reviews on the web

Field: **Protein Name**

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1: NP_038721 BLink, Domains, Links
tumor necrosis factor alpha; tumor necrosis factor-alpha; TNF alpha [Mus musculus]
gi|7305585|ref|NP_038721.1|[7305585]

2: AAL26919 BLink, Domains, Links
TNF-alpha [Canis familiaris]
gi|16588855|gb|AAL26919.1|AF327899_1[16588855]

3: JU0029 BLink, Domains, Links
tumor necrosis factor alpha precursor - rat
gi|92931|pir||JU0029[92931]

4: A25451 BLink, Domains, Links
tumor necrosis factor alpha precursor - rabbit
gi|90165|pir||A25451[90165]

5: JH0529 BLink, Domains, Links
tumor necrosis factor alpha precursor - sheep
gi|89907|pir||JH0529[89907]

6: S06192 BLink, Domains, Links
tumor necrosis factor alpha precursor - goat (fragment)
gi|89839|pir||S06192[89839]

7: JQ1344 BLink, Domains, Links
tumor necrosis factor alpha precursor - horse
gi|89136|pir||JQ1344[89136]

8: QWMSN BLink, Domains, Links
tumor necrosis factor alpha precursor - mouse
gi|69406|pir||QWMSN[69406]

9: CAA26669 BLink, Domains, Links
TNF-alpha [Homo sapiens]
gi|37210|emb|CAA26669.1|[37210]

☐ 10: AAF87741 BLink, Domains, Links
tumor necrosis factor alpha; TNF alpha [Capra hircus]
gi|9454281|gb|AAF87741.1|[9454281]

☐ 11: BAA13130 BLink, Domains, Links
TNF-alpha [Capra hircus]
gi|1483165|dbj|BAA13130.1|[1483165]

☐ 12: AAB49506 BLink, Domains, Links
tumor necrosis factor alpha; TNF-alpha [Trichosurus vulpecula]
gi|1881812|gb|AAB49506.1||bbm|391719|bbs|179895[1881812]

☐ 13: AAB32391 BLink, Domains, Links
tumor necrosis factor alpha; TNF-alpha [Canis familiaris]
gi|802045|gb|AAB32391.1||bbm|354002|bbs|157482[802045]

☐ 14: CAA68530 BLink, Domains, Links
tnf-alpha [Mus musculus]
gi|54832|emb|CAA68530.1|[54832]

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Exhibit B